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OPINION REVIEW

Reducing anastomotic leak in colorectal surgery: The old dogmas and the new challenges

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Abstract

Anastomotic leak (AL) constitutes a significant issue in colorectal surgery, and its incidence has remained stable over the last years. The use of intra-abdominal drain or the use of mechanical bowel preparation alone have been proven to be useless in preventing AL and should be abandoned. The role or oral antibiotics preparation regimens should be clarified and compared to other routes of administration, such as the intravenous route or enema. In parallel, preoperative antibiotherapy should aim at targeting collagenase-inducing pathogens, as identified by the microbiome analysis. AL can be further reduced by fluorescence angiography, which leads to significant intraoperative changes in surgical strategies. Implementation of fluorescence angiography should be encouraged. Progress made in AL comprehension and prevention might probably allow reducing the rate of diverting stoma and conduct to a revision of its indications.

Key words: Anastomotic leakage; Rectal surgery; Colic surgery; Prevention; Surgical site infection; Anastomosis; Complication

Core tip: The present manuscript reviews the current evidence regarding the prevention of anastomotic leak in colorectal surgery. Oral antibiotics and fluorescence angiography might help reduce the incidence of anastomotic leak. Study of the microbiome might offer interesting paths for research. Progress made in anastomotic leak comprehension and prevention might allow reducing the rate of diverting stoma and conduct to a revision of its indications.

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INTRODUCTION

Anastomotic leak (AL) refers to the communication between hollow viscera lumen and the peritoneal cavity at the anastomotic level[1]. Despite a lack of widely accepted consensus regarding the definition of AL[2,3], AL was documented to occur in 8.1% of patients after right hemicolectomy according to the 2015 ESCP snapshot audit[4], 6.4% after colonic cancer surgery according to a nationwide Danish study including 9’333 patients[5] and 11% after rectal cancer surgery as reported by a systematic review and meta-analysis pooling 84 studies[6]. AL is graded according to the therapeutic management it requires: Grade A (no management), grade B (non operative management), grade C (operative management)[3].

In addition to the septic complications and prolonged hospitalization induced, AL leads to delayed adjuvant chemotherapy or no chemotherapy at all[7]. Further, a recent systematic review and meta-analysis including 78’434 colorectal cancer patients showed that AL was associated with increased local recurrence [risk ratio (RR) 1.90] and reduced overall survival (RR 1.36)[8]. Another systematic review and meta-analysis including 11'353 rectal cancer patients demonstrated that AL led to increased local recurrence [hazard ratio (HR) 1.71] and decreased survival (HR 1.67) and cancer-specific survival (HR 1.03) after anterior resection[9].

Despite the human and financial costs generated by AL[10], and the efforts put in reducing its occurrence, the incidence of AL has not evolved among the last years. Further, pre-operative prediction of AL and identification of at-risk patients are not accurate enough[11], and AL is often diagnosed too late in the postoperative period[12]. In an effort to optimize the therapeutic care of patients with colorectal anastomosis with the hope to reduce the occurrence of AL, we will review old dogmas regarding prevention of AL and confront them to the most recent evidence, and will define the new challenges in the field.

PREOPERATIVE MEASURES TO PREVENT AL

Patient-related factors

A recent systematic review identified several adjustable and non-adjustable risk factors for AL, including male gender, smoking, obesity, alcohol, steroid and non-steroidal anti-inflammatory drugs, operative time, transfusion, contamination of the operative field and emergency surgery[13]. Further, albumin < 3.5 g/dL, anemia, hypotension and use of inotropes were reported to increase the risk of AL[14]. Preoperative radiotherapy was also documented to constitute a risk factor for AL[15], especially if surgery occurred within an interval of 11-17 d after radiotherapy[16]. Therefore, adjustable risk factors should be corrected before proceeding to a digestive anastomosis, in order to reduce the risk of AL. This can be partly done through enhanced recovery programs[17], whose implementation in colorectal surgery units led to decreased postoperative morbidity and length of stay[18]. However, the effect of enhanced recovery protocols on the rate of AL remains to be demonstrated.

Preoperative oral antibiotics and mechanical bowel preparation

Preoperative mechanical bowel preparation alone has lost in interest after multiple publications demonstrating its absence of benefit in reducing AL in elective colorectal surgery. Contant *et al*[19] randomized 1’431 patients to receive or not mechanical bowel preparation before elective colorectal surgery, and showed that patients who received mechanical bowel preparation did not have a lower rate of AL. Further, a systematic review and meta-analysis of randomized clinical trial (RCT) including 4’859 patients confirmed this finding[20].

Recently, authors, such as Scarborough[21], postulated that mechanical bowel preparation allowed to improve the delivery of oral antibiotic preparation to the bowel mucosa and could therefore not be assessed independently. Using the American College of Surgeons National Surgical Quality Improvement Program

database and including 4'999 patients, they showed that combined preoperative oral antibiotics and mechanical bowel preparation lowered the rate of AL from 5.7% to 2.8% in colorectal surgery when compared to patients not receiving any kind of preparation. However, neither oral antibiotics alone or MBP alone allowed to lower the rate of AL[21]. Further publications reached the same conclusions but used the same database[22,23]. However, latest studies using the same database only showed an effect of oral antibiotics alone and demonstrated that combination with MBP offered no additional advantage[24,25].

Therefore, a large RCT is needed to determine whether oral antibiotics alone and intravenous antibiotics are sufficient in reducing AL after colorectal surgery or whether association with mechanical bowel preparation is needed[26]. Furthermore, the type of MBP is very different among surgeon practice[27] and probably needs standardization before conclusion could be drawn from MBP studies. The use of rectal enema associated or not with antibiotics should be assessed; as evidence is growing that the local microbiome at the anastomotic site might be implicated in AL, as discussed below.

Microbiology

Recent evidence supports the hypothesis that AL might result from a local infective complication, resulting in impaired healing at the anastomotic level due to a local increase in collagenase activity. For instance, Shogan *et al*[28] showed in a rat model that *Enterococcus faecalis* led to the degradation of collagen IV at the anastomotic level through activation of MMP9. Further, topical antibiotherapy administered by enema targeting *Enterococcus faecalis* allowed to reduce AL to 0%, whereas intramuscular cefotixim—commonly used for elective surgery prophylaxis—did not reduce collagenase activity nor AL[28]. Moreover, a recent study using rat model of colo-colic anastomosis demonstrated that the selective MMP-8, MMP-9, and MMP-12 inhibitor AZD3342 allowed to maintain the anastomotis baseline breaking strength and to reduce AL[29]. Butyrate, a short-chain fatty acid, was shown to reduce AL[30-32], probably through its inhibitory effect on *Pseudomonas aeruginosa*[33]. In a case-control study including 8 patients with AL and 8 patients without AL after stapled colorectal anastomosis, van Praagh *et al*[34] showed that patients with AL had lower microbial diversity and higher abundance of *Lachnospiraceae*. They postulated that the higher rate of AL might be explained by the presence of mucin-degrading *Ruminococci* within that family[34]. Stumpf *et al*[35] found lower collagen type I/III ratio and higher expression of MMP-1, -2 and -9 in biopsies of patients with impaired anastomotic healing when compared to controls. These results suggest that unfavorable microbiome comprising collagenase-inducing pathogens might impair anastomotic healing and result in AL.

Further, anastomosis creation was shown to result in a 200- and 500-fold increase in the relative abundance of Enterococcus and Escherichia/Shigella, respectively, in a rodent model[36]. In a prospective multicentric cohort of patients undergoing colorectal surgery, including our center, Dubinsky-Pertzov *et al*[37] showed that carriers of beta lactamase-producing *Enterobacteriaceae* receiving cephalosporin-based antibioprophylaxis were at risk of surgical site infection [odds ratio (OR) 2.36]. These findings suggest that changes in the local microbiome caused by surgery or unappropriate prophylactic antibiotherapy might worsen the situation of patients with already unfavorable microbiome profiles. Also, radiotherapy was documented to change the composition of the microbiome[38,39], which constitutes a finding of importance for rectal cancer patients receiving neoadjuvant treatment but with no clear demonstration in increased AL so far.

Microbiome is a new and very promising field of research, especially when studying the aetiologies of AL in colorectal surgery. Identifying at risk patients with unfavorable microbiome, comprising pathogens with high collagenase activity, and treating them with appropriate antibiotic regimen (per os, intravenous or by enema) and/or faecal transplantation if required could help reducing AL rate. Further, studying the microbiome might help explaining the protective effect of preoperative oral antibiotics on the AL rate.

OPERATIVE MEASURES TO PREVENT AL

Surgical approach

The United States Nationwide Inpatient Sample database (including 244'129 elective colectomies) was analyzed to compare outcomes between robot-assisted colectomy (1'584 colectomies), laparoscopic colectomy (116'261 colectomies) and open colectomy (126'284 colectomies). AL was not reported, but the authors described laparoscopic

colectomy to lower the risk of complications (19.8% *vs* 33.2%) and stoma (3.5% *vs* 13.0%) when compared to the open approach. No difference could be found between laparoscopy and the robotic technique regarding these outcomes[40]. On the opposite, analysis of the The Danish Colorectal Cancer Group database described laparoscopic colectomy as a risk factor for AL (OR 1.34) in 9'333 patients[5]. Regarding right colectomies, a systematic review and meta-analysis including 7'780 patients found no difference in terms of AL between the laparoscopic and robotic approaches[41]. Regarding elective and emergency sigmoidectomy for diverticulitis, a Cochrane systematic review and meta-analysis of RCT did not describe any difference in terms of reoperation due to AL between patients with laparoscopic colectomy and those with open colectomy (349 pooled patients for that outcome)[42]. Further, the intermediate analysis of the ROLARR trial described no difference in AL rate between the two approaches for rectal cancer[43]. Regarding the latest, the transanal total mesorectum excision (taTME) technique, bypassing the anatomic limitations of the narrow pelvis, might allow to reduce AL, but remains to be evaluated for that outcome.

Anastomosis technique

Handsewn and stapled anastomoses are still widely performed according to surgeons preferences, reflecting the lack of consensus regarding the anastomotic method. A Cochrane systematic review and meta-analysis including 1'233 patients from 9 RCT found no difference in terms of AL, clinical AL and radiological AL between patients with stapled or handsewn colorectal anastomoses[44]. However, the authors did not perform subgroup analysis according to the underlying disease or to the presence or not of associated procedures (drainage, diverting stoma). Further, all included studies were anterior to 1995. In emergency procedures, another systematic review and meta-analysis did not identify any statistical differences between stapled and handsewn anastomoses (1'120 patients)[45].

Regarding right colectomy or ileo-cacecal resection, the 2015 ESCP audit described an AL rate of 8.1% among 3'208 patients. After adjustment for confounding factors, the use of a stapler was significantly associated with AL (OR 1.43)[4]. Further, stapled anastomoses were more frequently used in low risk patients, resulting in a likely underestimation of the risk of AL after right colectomy or ileo-caecal resection.

We should note that lower anastomoses are more at risk of AL, as known since decades[15,46]. A snapshot audit specifically concerning left colon, sigmoid and rectal resections is currently undergoing[47] and therefore conclusion cannot be reached regarding left colon and rectal surgery. No evidence is supporting either of the construction methods used for colorectal anastomosis (side to side, end to side, side to end, end to end). The evidence seems to be more straightforward regarding the number of catridges used for rectal division. A retrospective study from Austria demonstrated in 382 patients who benefited from rectal division using a linear stapler and colorectal anastomosis using a circular stapler or compression device, that the use of 3 or more cartridges increased the incidence of AL (19.4% AL in this subgroup)[48]. Further, the number of intersections of staple lines also correlated to the rate of AL in colorectal anastomosis using a double stapling technique[49]. A single stapling technique for colorectal anastomosis (in TaTME for example), in opposition with the conventional double stapling technique, was demonstrated to be safe in low anterior resection but lacks evidences in term of reduction of AL[50].

Compression anastomosis consists of a stapler equipped with disposable rings used for colorectal anastomosis: The rings are applied on each side at the anastomotic level and are evacuated into the stools once tissue necrosis and healing have occurred. A study performed in pigs with colorectal anastomoses showed that compression anastomosis was associated with less inflammation and scarring when compared with the stapling technique[51]. A retrospective multicentric study including 1'180 patients described an AL rate of 3.22% using the ColonRing device[52]. Further, a prospective postmarketing evaluation of the ColonRing described an AL rate of 5.3% among 266 patients, but a septic anastomotic complication rate of 8.3%, which could reflect the true AL rate[53]. A recent systematic review and meta-analysis including 10 RCT (1'969 patients) found no difference in terms of AL between patients with handsewn or stapled anastomosis (977 patients) and those with compression anastomoses (992 patients)[54]. Compression anastomosis has however not gained in popularity.

Intraoperative assessment of the anastomosis

As previously reported[55], many methods have been develop to perioperatively assess the integrity of colorectal anastomoses. Briefly, the air leak test, which consists in insufflating the bowel at the anastomotic level to detect any AL, was demonstrated to help identifying AL perioperatively and led to their repair, resulting in lower rate of postoperative AL[56,57]. Intraoperative endoscopy, in addition, to evaluate the

anastomosis integrity, allows identifying bleeding at the anastomotic level or disruption of the anastomosis[58]. However, it requires endoscopy skills, extra material, is time-consuming and requires further scientific validation in terms of AL prevention[59].

New methods rely on the assessment of the blood supply to the anastomosis. Adequate perfusion of the healing tissue is key to prevent AL, and a reduction in the blood flow at the rectal stump was shown to correlate with AL[60]. Historical methods include relying on the color of the bowel, as proposed by Goligher[61], or observing the pulsatile flow at the cut section, as stated by Novell and Lewis[62]. Objective and reliable methods assessing anastomosis vascularization have been developed since, as reported in our recent review[55], mentioning notably Doppler ultrasound[63] and light spectroscopy[64]. More recently, fluorescence perfusion angiography has showed a widespread clinical use. Briefly, a fluorophore is injected intravenously, excited by a specific wavelength to emit in another specific wavelength (usually infrared) just after vessel division an/or completion of the anastomosis, allowing the surgeon to identify any defect in vascularization at the anastomotic level. Jafari *et al*[65] reported that fluorescence perfusion angiography allowed to reduce AL from 18% to 6% after robotic–assisted anterior resection. Using a prospective cohort of 504 patients undergoing elective colorectal surgery with anastomosis, our team demonstrated that fluorescence perfusion angiography allowed for a change in the strategy of bowel division due to insufficient perfusion in 5.8% of patients, with no subsequent AL[66]. Results of the PILLAR II study documented a change in the surgical plan in 8% of 139 included patients undergoing anterior resection with no subsequent AL in those patients[67]. A recent systematic review and meta-analysis pooling 1’302 patients confirmed these results by reporting that fluorescence perfusion angiography reduced the rate of AL in patients operated for colorectal cancer[68].

Therefore, old methods allowing assessing the integrity of the anastomosis and the absence of AL should be combined to new technologies, such as fluorescence perfusion angiography, which aim at determining the vascularization of the anastomosis, a prerequisite to an efficient healing process without subsequent AL. New studies should aim at determining whether stimulation of the neoangiogenesis process, for example by the local administration of recombinant VEGF[69], could help in further reducing the occurrence of AL.

Diverting stoma

The creation of a lateral ileostomy or colostomy in patients at risk of AL aims at diverting the bowel content away from the anastomosis in order to decrease the rate of AL and the related morbidity. However, diverting stoma expose the patients to the risk of dehydration or to stoma closure-related complications. Further, they lead to an additional scare or won’t be closed in a significant proportion of patients[70].

A Cochrane systematic review and meta-analysis including RCT assessing the use of prophylactic stoma versus no stoma in patients with low anterior resection for rectal cancer until November 2009 described the use of covering stoma to lower the incidence of AL (RR 0.33)[71]. Thereafter, a review of 525 patients with colo-anal anastomosis from the NSQIP database identified the absence of stoma as a risk factor for developing postoperative sepsis (OR 6.29), although the rate of AL was not reported. Also, allocation to the stoma group was not randomized and the effect was not observed in patients with low pelvic anastomosis (1’266 patients)[72]. A systematic review and meta-analysis including all studies published between 2014 and 2017 regarding the role of a protective stoma in patients undergoing low anterior resection, identified the presence of a stoma as a protective factor against AL (RR 0.38, 5’612 patients, 11 studies)[73]. A later systematic review and meta-analysis including only RCT (4 RCT, 358 patients) confirmed that diverting stoma lowers the risk of AL (OR 0.32)[74]. The Cochrane collaboration produced a systematic review and meta-analysis pooling 648 patients from 6 RCT and identified diverting stoma as a protective factor against clinical AL (RR 0.33) after low anterior resection[71].

Evidence regarding “ghost ileostomy” – a bowel loop brought through the abdominal wall but left unopened, leaving the possibility to be transformed in an ileostomy if needed – is low and remains to be clarified[3]. Therefore, we can conclude that diverting stoma allows reducing the occurrence of AL in at-risk patients (those with low anastomosis). Ghost ileostomy could constitute a solution to avoid the occurrence of stoma-related complications, but it should be keep in mind that ghost ileostomy won’t allow to avoid AL but rather to decrease its morbidity.

Prophylactic intra-abdominal drainage

Prophylactic intra-abdominal drainage during elective colorectal surgery was thought to help monitoring the occurrence of AL and to reduce its morbidity by avoiding a generalized peritonitis. The GRECCAR 5 trial compared 236 randomized rectal cancer

patients allocated to the intra-abdominal drain group to 233 patients allocated to the group without drainage. Intra-abdominal drainage did not allow to reduce the rate of pelvic sepsis, the postoperative morbidity, the reoperation rate, the lenght of hospital stay and the rate of stoma closure[75]. Later, a systematic review and meta-analysis pooling 760 patients from 4 RCT demonstrated that intra-abdominal drainage did not reduce AL, pelvic complications, reintervention and mortality. Contrariwise, the incidence of postoperative bowel obstruction was significantly higher in the drained group (OR 1.61)[76]. A Cochrane systematic review obtained the same conclusion thtat prophylactic intra-abdominal drainage did not reduce the rate of AL[77]. Therefore, prophylactic intra-abdominal drainage should be discouraged in elective colorectal surgery.

Prophylactic transanal tube decompression

Prophylactic transanal tube decompression was thought to lower the risk of AL whilst presenting less risks of complication that diverting stoma. A systematic review and meta-analysis pooling 1'772 patients undergoing anterior resection described transanl tube decompression to lower the risk of AL (RR 0.44)[78]. However, patients receiving diverting stoma were excluded, leading to a potential underestimation of the AL rate. Another systematic review and meta-analysis followed, including patients with diverting stoma, and obtained the same conclusion (a reduction of the risk of AL (RR 0.42) in patients with transanal tube decompression)[79]. Therefore, prophylactic transanal tube decompression could constitute an efficient method to prevent AL in high risk patients without exposing them to the complications of diverting stoma. A well-conducted large scale RCT comparing the 2 techniques remains, however, to be conducted.

CONCLUSION

AL still constitutes a significant issue in colorectal surgery, and its incidence has remained stable over the last years. The use of intra-abdominal drain or the use of mechanical bowel preparation alone have been proven to be useless in preventing AL and should be abandoned. The role or oral antibiotics preparation regimens should be clarified and compared to other routes of administration, such as the intravenous route or enema. In parallel, the composition of the microbiome of patients with AL should be precisely determined, in order to identify patients at risk of AL and offer targeted preoperative antibiotics. AL can be further reduced by fluorescence angiography, which leads to significant intraoperative changes in surgical strategies. Implementation of fluorescence angiography should be encouraged. Progress made in AL comprehension and prevention might probably allow reducing the rate of diverting stoma and conduct to a revision of its indications.

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